Charles E. Lipsey (pro hac vice)
L. Scott Burwell (pro hac vice)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I Street, N.W., Suite 700
Washington, D.C. 20005-3315
Telephone: (202) 408-4000
Facsimile: (202) 408-4400

Thomas W. Banks (SBN 195006)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
245 First Street, 18th Floor
Cambridge, Massachusetts 02142
Telephone: (617) 444-8508
Facsimile: (617) 444-8608

WRIGHT & L'ESTRANGE
John H. L'Estrange, Jr. (SBN 49594)
Imperial Bank Tower, Suite 1550
701 "B" Street
San Diego, California 92101-8103
Telephone: (619) 231-4844

Attorneys for Defendant VYSIS, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

VYSIS' SUPPLEMENTAL STATEMENT OF DISPUTED FACTS IN OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

Date: November 19, 2001
Time: 10:30 a.m.
Place: Courtroom 1

Defendant Vysis, Inc. respectfully submits the following supplemental statement of disputed material facts, together with supporting evidence, in support of its Opposition to Gen-Probe's Motion for Partial Summary Judgment of Noninfringement Under the Doctrine of Equivalents.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
1. Vysis has previously admitted that TMA is a sequence-specific amplification method and does not use methods of non-specific amplification.	Vysis did not dispute this assertion in its opposition to Gen-Probe's April 30, 2001 Motion for Partial Summary Judgment.
2. All of the claims of the '338 patent incorporate an "amplification" element. The Court's June 20th Order confirms that each of those claims and incorporated amplification elements literally encompasses only non-specific amplification techniques.	The Court's construction of the claims of the '338 patent is a legal question, not a factual one. Vysis contends that the Court's resolution of that question of law is legally incorrect.
3. The differences between specific amplification methods and non-specific amplification methods are substantial.	Disputed. See Persing Decl., ¶¶ 5-16.
4. The methods do not perform the same function in the same way to achieve the same result.	Disputed. See Persing Decl., ¶¶ 5-16.
5. Gen-Probe's TMA method functions to exponentially increase both the **absolute** and **relative** amount of a particular nucleic acid sequence of interest in a mixture of nucleic	No dispute.

acids.	
6. In direct contrast, non-specific amplification functions only to increase the absolute amount of all nucleic acids present in a sample and does not increase the relative amount of a particular nucleic acid sequence of interest.	In the context of the claims of the '338 patent, the amplification step increases both the absolute and relative amount of the target nucleic acid present in the tested sample. See '338 patent; Mullis Dep. at 117.
7. Vysis' own expert has admitted the differences in function between specific amplification and non-specific amplification. [N]on-specific amplification techniques amplify all of the nucleic acid in a sample, both target and non-target nucleic acid. Specific amplification techniques, ***in contrast***, are intended to amplify only the target nucleic acid.	Vysis' expert has not opined that there is no difference between specific and nonspecific amplification techniques, but has the opinion that the differences are insubstantial. See Persing Decl. ¶¶ 5-16.
8. When a particular nucleic acid sequence of interest is contained in a mixture of nucleic acids in a clinical sample, TMA enables a person skilled in the art to exponentially copy the sequence of interest.	No dispute.
9. This makes it easy to determine whether or not a pathogenic microorganism is hiding	No dispute.

among millions of other organisms in a patient sample.	
10. Specific amplification is useful for diagnostic purposes even without a target capture step. In contrast, non-specific amplification is *not* a viable diagnostic method because it does not increase the amount of a target nucleic acid relative to everything else. Vysis' own expert witness has admitted this important distinction: Without the use of target capture prior to amplification, ***non-specific amplification would not be a viable technique for detecting target nucleic acids in a sample*** because, as pointed out in the quoted paragraph, non-specific amplification causes the replication of virtually any nucleic acid sequence, including other irrelevant nucleic acids in the sample.	Vysis disputes that non-specific amplification is "not a viable diagnostic method." Non-specific amplification is a viable diagnostic method when used in the context of claims of the '338 patent. May 25, 2001 Persing Decl., ¶ 11.
11. Therefore, Dr. Persing has admitted that "without the invention [i.e., the combination of a preliminary "target capture" step with amplification], ***only specific amplification could be used***."	Vysis disputes that the quoted section of Dr. Persing's May 25, 2001 Declaration was based on the assertions in Gen-Probe's Undisputed Fact No. 10.

12. The enzymes and primers used in any amplification process can be specific or non-specific.	No dispute.
13. The primers used in Gen-Probe's specific TMA amplification method have been carefully selected by Gen-Probe's scientists and are generally designed to bind to specific, unique sequences in a DNA or RNA molecule.	No dispute.
14. In amplification processes, sequence-specific primers and enzymes such as those used in TMA play a role substantially different from non-specific primers and enzymes.	Disputed. See Persing Decl., ¶¶ 10-16.
15. This fact is well known to those of ordinary skill in the art.	Disputed. See Persing Decl., ¶¶ 10-16.
16. For example, specific primers and enzymes can function together to amplify a target nucleic acid only if the specific sequence of interest bound by the primer and/or recognized by the enzymes is present	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.

in the sample.	
17. By contrast, non-specific primers and enzymes will amplify *any* and *all* sequences present in the sample.	No dispute.
18. The random primers will bind to all of the sequences in the sample and non-specific replication enzymes will catalyze DNA synthesis at points throughout the entire lengths of the nucleic acid molecules present without regard to sequence.	No dispute.
19. In its TMA method, Gen-Probe uses two amplification enzymes that depend upon the presence of specific primers.	No dispute.
20. One of these enzymes is reverse transcriptase ("RT").	No dispute.
21. RT is a DNA polymerase that produces a complementary DNA strand copy of a single-stranded RNA or DNA that has a bound primer.	No dispute.
22. In TMA, RT produces complementary DNA from the target nucleic acids (or their	No dispute.

complementary strands) only if the sequence-specific primers first bind to a single strand of RNA or DNA.	
23. If the target organism is not present in the sample, the primers will be unable to bind to the captured sequence and the RT will not initiate synthesis.	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.
24. Another specific primer used in Gen-Probe's method also includes a specific "promoter" sequence that is recognized by another enzyme ("T7 RNA polymerase") that binds specifically to that promoter sequence to produce many RNA copies by transcription.	No dispute.
25. A function "T7 promoter" is formed in the course of the TMA process if, and only if, (1) the primer finds and binds to its complementary target sequence in the captured target molecule so that the target sequence is copied by reverse transcriptase and (2) the second primer binds to the newly synthesized DNA and DNA polymerase	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.

makes the complementary DNA strand.	
26. If this double-stranded, and hence functional, T7 promoter *is* formed as a result of these *two* primer binding and extension processes, then the T7 RNA polymerase used in Gen-Probe's HIV/HCV test will amplify the sequence attached to the T7 promoter sequence.	No dispute.
27. The T7 RNA polymerase does not amplify other sequences present in the sample because they are not attached to a T7 promoter sequence.	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.
28. Thus, in Gen-Probe's HIV/HCV test, the T7 polymerase enzyme *specifically* recognizes the T7 promoter sequence, which has been *specifically* attached to the target sequence by the binding of *specific* primers, and the T7 polymerase *specifically* amplifies only that sequence.	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.
29. The process repeats in a cyclic fashion, only amplifying the particular target sequence	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity.

of interest.	See Persing Decl., ¶ 6; Mullis Dep. at 75.
30. Gen-Probe's amplification method therefore safeguards against amplification of non-target sequences and thus protects against false positive results.	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.
31. TMA functions in way that is substantially different than the way in which non-specific amplification functions.	Disputed. See Persing Decl., ¶¶ 9-16.
32. Specific amplification methods commonly achieve ***exponential*** amplification of the target sequence, as compared with linear amplification.	Disputed. Specific amplification methods can achieve either linear or exponential amplification, depending on the reaction conditions and the techniques employed. See Mullis Dep. at 102-03
33. Sustained, significant, exponential amplification is a hallmark of specific amplification methods.	Disputed. Specific amplification methods can achieve either linear or exponential amplification, depending on the reaction conditions and the techniques employed. See Mullis Dep. at 102-03.
34. In contrast, the non-specific amplification methods of Examples 4 and 5 of the '338 patent admittedly achieve only linear	No dispute.

amplification, not exponential amplification.	
35. The non-specific amplification methods of Examples 5 and 6 also cannot achieve exponential amplification. Because random primers bind at various places along the nucleic acids present in the sample, the products of amplification are fragmented.	Disputed. Example 6 of the '338 patent discloses a technique for achieving exponential amplification of a target nucleic acid. ('338 patent, col. 31, line 55 to col. 32, line 7.)
36. If these products were then subjected to another round of non-specific amplification, the resulting products would be smaller still.	Disputed.
37. Multiple rounds of non-specific amplification thus diminish rapidly in efficiency, whereas multiple rounds of specific amplification produce extraordinarily large amounts of full size product nucleic acids in very short periods of time.	Disputed. All nucleic acid amplification techniques have some degree of nonspecificity. See Persing Decl., ¶ 6; Mullis Dep. at 75.
38. Non-specific amplification using random hexamer primers results in fragmented nucleic acids, each of which contains the random sequences present in the primers.	No dispute.

39. The resulting products are thus heterogeneous and have undefined composition.	Disputed.
40. Such nucleic acids are unsuitable for most of the purposes for which homogeneous, specifically amplified nucleic acids of known composition are employed.	Disputed. In the context of the claimed invention, non-specific amplification techniques can amplify target nucleic acids in a manner sufficient to permit their detection as part of a diagnostic assay.
41. As a result, Gen-Probe's TMA method also does not yield the same result as that obtained with non-specific amplification.	Disputed. See Persing Decl., ¶¶ 9-16.
42. The Court has previously noted that the specification of the '338 patent contains no reference to any specific amplification techniques. To the contrary, the specification clearly suggests that the claimed amplification techniques of the invention don't require the use of specific primers necessary for specific amplification.	Vysis disputes the implication that specific amplification techniques are excluded from the claims of the '338 patent.

43. This absence in the '338 patent of any disclosure of specific amplification techniques was not accidental or unintended. To the contrary, Gene-Trak Systems, Vysis' predecessor-in-interest, and its employed inventors were well aware of the specific amplification techniques such as PCR. In fact, the admitted focus of the inventors' effort leading to the disclosure in the '338 patent was to find something "different" from specific amplification. For example, inventor Jon Lawrie testified that the patent was meant to cover new amplification methods using non-specific primers, not already-known methods such as PCR: Q. Can you recall any reason that a reference to PCR might have been intentionally omitted from the patent application? A. Yes.... Q. If there's no reference in the ['338] patent to combining target capture with PCR, do you have any explanation as to why it is not there?	Vysis disputes there is an absence of any disclosure of specific amplification in the '338 patent. Vysis does not dispute that Dr. Lawrie made the quoted statements in his deposition, but disputes the relevance of those statements to the determination of infringement under the doctrine of equivalents.

A. I believe that it was a separate, the thought behind this [referring to the '338 patent] was coming up with new methods of amplification, not old ones. Q. For the purposes of what you just said you classify PCR as an old method of amplification? A. PCR itself was described in the patent, issued patent [e.g., it was an "old" method]. Q. And your understanding of the 338 patent was that it was directed to other methods of amplification? A. The, it was, it was directed to the methods disclosed by, you know, the *methods separate from PCR.*	
44. Inventor King also stated the inventors' purpose and also distinguished non-specific amplification from PCR: Q. From a high level perspective, what were the discussion topics	Vysis does not dispute that Dr. King made the quoted statements in his deposition, but disputes the relevance of those statements to the determination of infringement under the doctrine of equivalents.

addressed during this meeting? A. I think that at the highest level we were looking for amplification methods ***that did not involve PCR amplification***. (King Depo. At 45:10-15 (emphasis added).) Q. Okay. So the purpose -- the general purpose of the discussion as I understand it that took place at Gene-Trak among the four doctors was to identify -- in general identify an amplification technique that would amplify low concentrations of target nucleic acids in a sample, correct? A. Yes. Q. And as I understand your testimony, you wanted to find a technique ***that was different from PCR***, correct? A. Yes.	doctrine of equivalents.
45. As this testimony suggests, PCR was well known to the inventors and the scientific	No dispute.

community at large. Dr. Kary Mullis invented PCR in 1983, for which he received the Nobel Prize in Chemistry. Dr. Mullis and his colleagues publicly described PCR at a scientific meeting in the summer of 1985 and published their discovery in December 20, 1985.	
46. James Richards, Gene Trak's Director of Business Development and Licensing, admits that, within the scientific community, PCR was immediately "big news."	No dispute.
47. One of the reasons that the '338 inventors sought to find something "different" from specific amplification techniques such as PCR was due to Gene Trak's concern that it could not obtain a license from Cetus Corp. to use PCR. Cetus Corporation, which employed Dr. Mullis, originally owned the rights to PCR. Gene-Trak sought a license from Cetus, but its requests were rejected.	No dispute.
48. The view of the fundamental difference between non-specific and specific	Vysis disputes the statement that there is a "fundamental difference between non-specific

amplification techniques was shared not only between the inventors but with Gene-Trak scientific management as well. In particular, in a letter he wrote in 1989, Dr. Richards, pointedly contrasted the '338 patent's method of non-specific amplification with other known specific methods that used specific primers or promoters: Cetus, Sibia/Salk, Biotechnica, etc. all claim specific primers for amplification *whereas the present invention claims uses of the* opposite, namely, non-specific primer or promoters....	and specific amplification techniques." See Persing Decl., ¶¶ 5 -16. Vysis also disputes that the independent claims of the '338 patent ever recited non-specific primers or promoters.

Date: November 8, 2001

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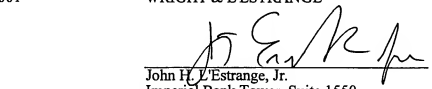

John H. L'Estrange, Jr.
Imperial Bank Tower, Suite 1550
701 "B" Street
San Diego, California 92101-8103

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